REMARKS

Claims 1, 2 and 4-17 currently appear in this application. The Office Action of August 1, 2003, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicants respectfully request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Claims 1, 4-6 and 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP3264532, hereinafter Teijin, in view of U.S. 4693892, hereinafter Hegasy et al., JP63-166824, hereinafter Yamada, and JP6321564, hereinafter Toyo.

This rejection is respectfully traversed. As disclosed in the specification as filed at page 1, beginning at line 21, all of the effective vitamin D3 compounds are unstable to light and heat. The present invention is directed to soft capsules for vitamin D3 which preserve the activity of the vitamin D3 compound by shielding the vitamin D3 compound from the effects of light, using a combination of titanium oxide and yellow iron oxide and/or red iron oxide, or titanium oxide and caramel. It was found that these combinations in the soft capsule formulations maintain the effectiveness of the vitamin D3 when it is encapsulated.

As described in lines 1-2 of the Abstract of XP-002205586, Teijin relates to an agent for treating alveolar bone atrophy, which agent contains active vitamin D3. The English translation of Teijin, submitted herewith, confirms that this document only states that the active ingredients may be formulated in a known manner into oral preparations, (e.g., soft capsules, hard capsules, tablets, syrups), injections or external preparations in combination with appropriate excipients, etc. (translation, page 4, first full paragraph). That is, Teijin merely discloses that active vitamin D3 can be formulated into conventional soft capsules. There is no recognition that vitamin D3 may not be stable to heat and/or light, nor that there is a method for making more stable soft capsules. Therefore, Teijin discloses nothing that would suggest the present invention to one skilled in the art.

Hegasy et al. add nothing to Teijin, as Hegasy et al. disclose light-fast capsules for dihydropyridines. These capsules are formed of gelatin colored with a mixture of beta-carotene and iron oxide. In the disclosure of Hegasy et al. it is the combination of beta-carotene and iron oxide which provides the light-fastness to the capsules. In fact, Hegasy et al. specifically disclose that if titanium oxide is used as an opacifying agent with beta-carotene, the instability is increased. The iron oxide is added to beta-carotene to

provide an improved capsule, and titanium dioxide is present only as an opacifying agent, not as an active ingredient in imparting light stability. Hegasy et al. require the presence of beta-carotene in the capsules, which is not present in the herein claimed invention.

Yamada merely teaches a triglyceride as a carrier for the active vitamin D3 compound. Toyo teaches that caramel having a light-transmittance of 15-60% at 310 nm wavelength and an amino acid can be used to provide a light-shielding gelatin capsule. There is nothing in Toyo that would lead one skilled in the art to combine caramel with a titanium oxide.

Claims 2, 7-9 are rejected under U.S.C. 103(a) as being unpatentable over Teijin in view of JP55141242, hereinafter Parke-Davis, Hegasy et al., and Toyo.

This rejection is respectfully traversed. As noted above, Teijin merely states that vitamin D3 compounds can be formulated into soft capsules, but there is no disclosure of the components of the soft capsules or whether there is present in the capsules any component to make the capsules light-fast. Parke-Davis discloses a gelatin capsule which is colored by caramel and condensed phosphate, to which titanium dioxide is optionally added. The capsules of the present invention do not contain condensed phosphate, so this patent adds nothing to Teijin. Hegasy et al. teaches the combination

of beta carotene and iron oxide for capsules, and Toyo requires the presence of an amino acid with the caramel to form a stable gelatin capsule.

The Examiner has shown no motivation to combine the cited references in order to obtain the present invention. As shown in the specification as filed in the Examples and Comparative Examples, the individual components of titanium oxide, iron oxide, and caramel, do not provide the degree of light fastness to soft capsules as the claimed combinations, *i.e.*,

A soft capsule formulation comprising an oily solution of an active vitamin D3 compound; and a soft capsule shell which contains (a) titanium oxide and (b) yellow iron oxide and/or red iron oxide, and encapsulates the oily solution of the active vitamin D3 compound; or

A soft capsule formulation comprising an oily solution of an active vitamin D3 compound; and a soft capsule shell which contains (1) titanium oxide and © caramel, and encapsulates the oily solution of the active vitamin D3 compound.

The present invention is based on the finding that the light stability of an active vitamin D3 compound encapsulated in a capsule is remarkably increased by using the components (a) titanium oxide and (b) yellow iron oxide and/or

red iron oxide, or the components (a) titanium oxide and (c) caramel in the capsule shell. This combination cannot be inferred from citations which disclose the use of components (a), (b), or (c) alone.

As the Federal Circuit stated in *In re Lee*, 61 USPQ2d 1430 (January 18, 2002, Fed. Cir.), "As applied to the determination of patentability *vel non*, when the issue is obviousness, 'it is fundamental that rejections under 35 U.S.C. 103 must be based on evidence comprehended by the language of that section.' *In re Grasselli*, 53 USPQ2d 1769, 1774 (Fed. Cir. 2000)... When patentability turns on the question of obviousness, the search for an analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness *See, e.g., McGinley v. Franklin Sports, Inc*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) ('the central question is whether there is a reason to combine [the] references,' a question of fact drawing on the *Graham* factors."

'The factual inquiry whether to combine references must be thorough and searching.' *Id.* This precedent has been reinforced in myriad decisions, and cannot be dispensed with, *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000). ('a showing of

a suggestion, teaching, or motivation to combine the prior art references is an "essential component of an obviousness holding"') (quoting *C. R. Bard, Inc. v. M3 Systems, Inc.* 48 USPQ2d (Fed. Cir. 1998)) The Court went on to quote *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999), "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."

There is a requirement for specificity in combining references, *See, In re Kotzab*, 55 USPQ2d 13134, 1317 (Fed. Cir. 2002)("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.").

In the present case, the Examiner has shown no motivation to combine the cited references to arrive at the particular invention claimed herein.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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1. Title of the Invention

Active vitamin D-containing therapeutic agents

2. Claims

(1) A therapeutic agent for alveolar bone atrophy, which comprises an active vitamin D as an active ingredient.

(2) The therapeutic agent for alveolar bone atrophy according to claim 1, wherein the active vitamin D is selected from the group consisting of 1α-hydroxyvitamin D, 1α,24-dihydroxyvitamin D, 1α,25-dihydroxyvitamin D, 1α,24,25-trihydroxyvitamin D, 24,24-difluoro-1α,25-dihydroxyvitamin D, 26,26,26,27,27,27-hexafluoro-1α,25-dihydroxyvitamin D, 25-hydroxyvitamin D_3-26,23-lactone and 1α,25-dihydroxyvitamin D_3-26,23-lactone.

3. Detailed Description of the Invention

<Technical Field>

The present invention relates to therapeutic agents for alveolar bone atrophy.

<Prior Art>

When attacked by periodontal disease (commonly called pyorrhea alveolaris), patients experience bone resorption starting from the alveolar crest. When bone atrophy progresses to more advanced stages with increasing bone resorption, tooth-supporting periodontal tissues including alveolar bone are damaged even where teeth per se are completely intact. Consequently, the teeth become less stable and move too easily; and eventually, in most cases, there is no choice but to pull out the teeth. For this reason, there is a need to develop a therapeutic agent for preventing or ameliorating alveolar bone atrophy.

However, such an agent for treatment of alveolar bone atrophy in patients with periodontal disease has been completely unknown.

On the other hand, it has been found that 1α-hydroxyvitamin D, which is a member of active vitamins D, is effective in treating and/or preventing osteoporosis, chronic renal failure-induced bone lesions, hypoparathyroidism and osteomalacia. However, its effect on alveolar bone atrophy has been completely unknown.

<Problems to be Solved by the Invention>

Under the circumstances, the inventors of the present invention first focused on the MD method widely used as an assessment of bone atrophy level in the field of orthopedics, and adapted this method for assessing the level of alveolar bone atrophy to develop an assessment strategy for alveolar bone atrophy (JP 62-266053 A, published on November 18, 1987).

Further, the inventors of the present invention made extensive and intensive efforts to develop a therapeutic agent for alveolar bone atrophy using such an assessment strategy for alveolar bone atrophy. As a result, they found that active vitamins D were effective in treating alveolar bone atrophy, and then arrived at the present invention.

<Means for Solving the Problems>

Thus, the present invention provides a therapeutic agent for alveolar bone atrophy, which comprises an active vitamin D as an active ingredient.

The term "active vitamin D" as used herein encompasses active vitamin D_2, active vitamin D_3 and derivatives thereof. Specific examples include 1α-hydroxyvitamin D, 1α,24-dihydroxyvitamin D, 1α,25-dihydroxyvitamin D, 1α,24,25-trihydroxyvitamin D, 24,24-difluoro-1α,25-dihydroxyvitamin D, 26,26,26,27,27,27-hexafluoro-1α,25-dihydroxyvitamin D,

25-hydroxyvitamin D_3-26,23-lactone and 1α,25-dihydroxyvitamin D_3-26,23-lactone. Above all, preferred are 1α-hydroxyvitamin D_3, 1α,24(R)-dihydroxyvitamin D_3 and 1α,25-dihydroxyvitamin D_3.

These active ingredients may be formulated in a known manner into oral preparations (e.g., soft capsules, hard capsules, tablets, syrups), injections or external preparations in combination with appropriate excipients, etc.

Examples of such excipients include vegetable oils (e.g., corn oil, cottonseed oil, coconut oil, almond oil, peanut oil), oily esters (e.g., medium chain fatty acid glycerides), mineral oils, petrolatum, animal fats and oils, cellulose derivatives (e.g., crystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), polyvinylpyrrolidone, dextrin, lactose, mannitol, sorbitol and starch.

The active ingredients are usually administered at a dose of 0.01 to 10 μg/day/person, preferably 0.25 to 4.0 μg/day/person, usually given in one to three divided doses per day. The active ingredients are preferably formulated such that the resulting formulations satisfy such a dosage requirement.

The method of the present invention may also be used in combination with existing therapeutic agents available as drug therapy.

The present invention will be further described in the

following Example.

[Example]

Two groups of patients with periodontal disease (Cases A and B) were tested as described in JP 62-266053 A. Four incisors on the lower jaw between the left and right second incisors were radiographed together with an aluminum step-wedge (5 steps, 5 mm/step) (minimum: 5 mm; maximum: 25 mm). The shadow density at a site one-third from the root apex of the central incisor was measured using a microdensitometer and then recorded on a chart at 5-fold magnification. The shadow density of the aluminum step-wedge was also measured and recorded. In the same manner as described in JP 62-266053 A, the charts were used to calculate the alveolar bone width d, the absorption area ΣGS (expressed as the number of steps on the aluminum step-wedge) and the maximum absorbance GS_{max} at the following sites:

L_2-L_1: a site between the second and first incisors at the left side;

L_1-R_1: a site between the first incisor at the left side and the first incisor at the right side; and

R_1-R_2: a site between the first and second incisors at the right side. These measured values were used as the values before administration.

After starting administration of 1α-hydroxyvitamin D_3 at a dose of 1.0 μg/day, the patients were measured for d, ΣGS and

GS_{max} every 2 to 5 months in the same manner as described above. The % change versus before administration [(after administration - before administration)/before administration × 100] was scored as follows: change within ± 10% = 0, increase over 10% = −1, and decrease over 10% = +1. The total scores of d, ΣGS and GS_{max} were each assessed as follows: amelioration for a score of 3 to 2, no change for a score of 1 to −1, and deterioration for a score of −2 to −3.

The test results, scores and assessment results are shown for each site in Table 1 (Case A) and Table 2 (Case B).

In Case A, amelioration effects were observed at all sites from 5 to 8 months after starting administration, and they were also maintained for a further period. In Case B, amelioration effects were observed at all sites from 5 months after starting administration, and they were also substantially maintained for a further period.

Table 1 (Case A)

1) L_2-L_1

	Measured value			Total score	Assessment
	d	ΣGS	GS_{max}		
Before administration	10.9	0.80	0.62		
3 months after administration	12.1	0.80	0.49	0	No change
5 months after administration	10.9	0.46	0.42	2	Amelioration
16 months after administration	6.8	0.29	0.41	3	Amelioration
22 months after administration	7.5	0.48	0.49	3	Amelioration

2) L_1-R_1

	Measured value			Total score	Assessment
	d	ΣGS	GS_{max}		
Before administration	20.8	1.44	0.72		
3 months after administration	18.9	1.34	0.63	1	No change
5 months after administration	20.1	1.59	0.71	-1	No change
16 months after administration	18.0	0.54	0.54	3	Amelioration
22 months after administration	19.2	1.15	0.56	2	Amelioration

3) R_1-R_2

	Measured value			Total score	Assessment
	d	ΣGS	GS_{max}		
Before administration	10.8	1.01	0.73		
3 months after administration	13.0	0.83	0.54	1	No change
5 months after administration	9.8	0.71	0.59	2	Amelioration
16 months after administration	9.0	0.35	0.46	3	Amelioration
22 months after administration	9.9	0.72	0.59	2	Amelioration

Table 2 (Case B)

1) L_2-L_1

	Measured value			Total score	Assessment
	d	ΣGS	GS_{max}		
Before administration	8.0	0.40	0.48		
5 months after administration	5.2	0.25	0.44	2	Amelioration
9 months after administration	8.7	0.28	0.41	2	Amelioration
19 months after administration	5.7	0.28	0.33	3	Amelioration
27 months after administration	6.1	0.32	0.52	2	Amelioration

2) L_1-R_1

	Measured value			Total score	Assessment
	d	ΣGS	GS_{max}		
Before administration	9.3	0.88	0.82		
5 months after administration	8.0	0.59	0.61	3	Amelioration
9 months after administration	10.5	0.54	0.54	1	No change
19 months after administration	8.6	0.44	0.49	2	Amelioration
27 months after administration	9.3	0.72	0.76	1	No change

3) R_1-R_2

	Measured value			Total score	Assessment
	d	ΣGS	GS_{max}		
Before administration	7.7	0.98	0.85		
5 months after administration	5.7	0.36	0.65	3	Amelioration
9 months after administration	5.3	0.35	0.46	3	Amelioration
19 months after administration	2.7	0.20	0.32	3	Amelioration
27 months after administration	4.6	0.47	0.78	2	Amelioration

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1. Title of the Invention

Active vitamins D_3-contaning formulations

2. Claim

A hard capsule formulation of an active vitamin D_3, which comprises:

a solution or suspension of the active vitamin D_3 in a medium chain fatty acid triglyceride substantially free from unsaturated acids; and

a hard capsule shell with an average wall thickness of 70 μm to 75 μm at the cap shoulder,

wherein said hard capsule shell encapsulates said solution or suspension and receives band sealing.

3. Detailed Description of the Invention

(Technical Field)

The present invention relates to hard capsule formulations comprising stabilized active vitamins D_3 as active ingredients.

(Prior Art)

It is known that vitamins D_3 are converted into active vitamins D_3 through hydroxylation at the 25-position in the liver or at the 1-position in the kidney, thus exhibiting high physiological activity.

Examples of such physiological activity include stimulation of Ca absorption in the small intestine, stimulation of phosphate absorption as well as Ca absorption, and stimulation of bone resorption from bone tissue in cooperation with parathyroid hormone. For clinical use, active vitamins D_3 are known as therapeutic agents for chronic renal failure, hypoparathyroidism, osteoporosis or osteomalacia.

However, these active vitamins D_3 have the property of being unstable to air, light, heat, etc., and many contrivances are necessary to provide stable formulations of active vitamins D_3. Namely, to stabilize these active vitamins D_3, there various techniques are disclosed: for example, dissolving active vitamins D_3 into an oily base such as medium chain fatty acid triglycerides and encapsulating it together with dibutyl hydroxyanisole as a stabilizer gives soft capsule formulations

(JP 57-40414 A); and incorporating a UV absorber into capsule shells gives light-screening soft capsule formulations (JP 57-45415 B). Also disclosed are techniques using an antioxidant. However, the toxicity of such an antioxidant or UV absorber cannot be neglected. Further, when a medium chain fatty acid triglyceride used as an oily base is encapsulated in hard capsules, the capsule shells become brittle over time, thereby possibly causing leakage of the active ingredient. Also, the encapsulated ingredients are less viscous (20 C.P.) and easily leak from the joints of closed capsules. These events give rise to problems disadvantageous in providing formulations.

(Problems to be Solved by the Invention)

Thus, the present invention provides active vitamins D_3-containing hard capsule formulations capable of inhibiting time-dependent decrease in the potency of active vitamins D_3 without using a stabilizer as well as capable of preventing embrittlement and joint leakage in capsules even using a medium chain fatty acid triglyceride as a low-viscosity oily base.

(Means for Solving the Problems)

The inventors of the present invention have focused on the phenomenon that active vitamins D_3 remain stable for a long period of time when dissolved or suspended in a medium chain fatty acid triglyceride free from unsaturated acids. However, in the case of using such a high-purity medium chain fatty acid triglyceride,

serious embrittlement would occur in hard capsule shells and could lead to capsule breakage and/or joint leakage in the capsules. As a result of extensive and intensive efforts made to overcome these problems, the inventors of the present invention have found that stable hard capsule formulations can be obtained by using a particular type of hard capsule shell in combination with band sealing and by encapsulating in the capsule shell a solution or suspension of an active vitamin D_3 in a medium chain fatty acid triglyceride free from unsaturated acids. This finding led to the completion of the invention.

Examples of active vitamins D_3 used herein include those having a hydroxy group at the 1α-position such as 1α-hydroxyvitamin D_3, 1α,25-dihydroxyvitamin D_3, 1α,24-dihydroxyvitamin D_3, 1α,24,25-trihydroxyvitamin D_3, 1α-hydroxy-24-oxovitamin D_3, 1α-hydroxy-26,26,26,27,27,27-hexafluorovitamin D_3 and 1α-hydroxyvitamin D_3-26,23-lactone, as well as those having no hydroxy group at the 1α-position such as 24,25-dihydroxyvitamin D_3, 24-hydroxyvitamin D_3, 25-hydroxyvitamin D_3 and vitamin D_3-26,23-lactone. The hard capsule formulation of the present invention may encapsulate one or more of these active vitamins D_3. These active vitamins D_3 are known compounds and can be prepared in a known manner.

The term "medium chain fatty acid triglyceride free from

unsaturated acids" refers to a triglyceride of a straight-chain saturated fatty acid containing 6 to 14 carbon atoms. Examples of such a fatty acid include caproic acid (C6), caprylic acid (C8), capric acid (C10), lauric acid (C12) and myristic acid (C14), each of which is neither branched nor unsaturated.

The medium chain fatty acid triglyceride used herein is substantially free from unsaturated acids, for example, which is commercially available from Kao Corporation under the trade name of Coconad MT, Coconad RK or Coconad MT-N. Their properties will be shown below.

Trade name	Coconad RK	Coconad MT	Coconad MT-N
Ingredient	C_8 acid triglyceride	C_8/C_{10} acid triglyceride	C_8/C_{10} acid triglyceride
Appearance (normal temperature)	Colorless and transparent liquid	Colorless and transparent liquid	Colorless and transparent liquid
Specification			
Hue (APHA)	≤ 100	≤ 100	≤ 100
Acid value	≤ 0.3	≤ 0.1	≤ 0.1
Saponification value	345-365	340-360	335-350
Iodine value	≤ 4	≤ 1	≤ 1
Water content	≤ 1%	≤ 1%	≤ 1%
Indication	Edible fat	Edible fat	Edible fat

(Fatty acid and triglyceride composition)

Fatty acid composition (%)

	C_6	C_8	C_{10}	C_{12}	C_{14}
Coconad RK	0.5	97.3	2.2	---	---
Coconad MT	0.3	81.6	17.4	0.4	---
Coconad MT-N	0.1	74.7	24.7	0.2	0.3

Triglyceride composition (%)

	C_{22}	C_{24}	C_{26}	C_{28}	C_{30}
Coconad RK	0.1	97.1	1.6	---	---
Coconad MT	0.8	60.0	30.7	5.7	0.3
Coconad MT-N	---	46.0	40.0	11.0	---

In the hard capsule formulation of the present invention, hard capsule shells encapsulate the above active vitamins D_3 dissolved or suspended in the above triglyceride at a concentration of 0.00008% to 0.04% by weight. The solution or suspension of active vitamins D_3 is usually encapsulated in a volume of 50 to 250 μl per capsule.

Gelatin hard capsule shells used herein are break-proof ones which have a larger wall thickness at the cap shoulder than commercially available hard capsule shells in order to prevent embrittlement. The average wall thickness at the cap shoulder is about 64 μm to about 67 μm in capsule shells prepared in a usual manner, whereas it is about 70 μm to about 75 μm in the break-proof gelatin hard capsule shells used herein. Such a large wall thickness is advantageous in preventing capsule breakage. In addition, to meet the requirement for light stability, the gelatin hard capsule shells may contain colored pigments (e.g., edible tar-based dyes, iron red) or opacifiers (e.g., titanium white), which are used alone or in combination.

The hard capsule formulation of the present invention may be prepared by encapsulating the above triglyceride solution or suspension of active vitamin D_3 into the above hard capsule shells and then providing the closed capsules with band sealing at the joints. The band sealing may usually be provided at a thickness of 50 μm to 150 μm and at a band width of 1 mm to 3 mm using gelatin,

hydroxypropylcellulose, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or the like.

(Effects of the Invention)

The active vitamins D_3-containing hard capsule formulation of the present invention enables long-term stabilization of the active vitamin D_3 as an active ingredient and also ensures high stability of hard capsule shells. It is also characterized by its very simple preparation.

(Examples)

The present invention will be further described in the following Examples, which are not intended to limit the scope of the invention.

Reference Example-1

To confirm the embrittlement of hard capsule shells, 100 mg of caproic acid (C6), a medium chain fatty acid, was encapsulated in break-proof hard capsule shells and commercially available hard capsule shells, each of which contained White No.5. An aqueous solution (50°C) containing 22% gelatin and 2% Polysorbate 80 was then applied to the joints of the individual closed capsules in an amount of 12 to 15 mg (using a band sealer HICAPSEAL, Japan Elanco Company Ltd.) and dried at room temperature for 5 minutes under an air stream to prepare samples. The average wall thickness at the cap shoulder was about 73 μm in the break-proof hard capsule shells and 65 μm in the

commercially available hard capsule shells.

Each sample thus prepared was stored separately in a transparent glass bottle at room temperature and tested periodically using a pressure tester for capsule breakage (pressurized section: 20 mm in diameter; pressure: 5 kg) to confirm occurrences of capsule breakage. Table 1 shows the results obtained.

Table 1: Embrittlement of hard capsule shells

(20 capsules used for each test)

Days of storage	Inventive break-proof hard capsule shell	Commercially available hard capsule shell
1 day	0/20	5/20
15 days	0/20	4/20
30 days	0/20	7/20

In the case of encapsulating caproic acid (C6) alone contained in a medium chain fatty acid triglyceride(?), the commercially available capsule shells became brittle and easy to break. In contrast, no breakage was observed in the break-proof hard capsule shells.

Example-1

1α-Hydroxycholecalciferol (5 mg) was dissolved in Coconad MT (500 g, Kao Corporation) in the dark under a nitrogen gas stream without UV irradiation. This solution was encapsulated in a

routine manner into the above break-proof hard capsule shells containing White No.5. Band sealing was provided in the same manner as shown in Reference Example-1 to give a hard capsule formulation according to the present invention.

For comparison purposes, a conventional fat base (ODO, a medium chain fatty acid triglyceride available from The Nisshin Oil Mills, Ltd.) and peanut oil, a typical vegetable oil, were used instead of Coconad MT to prepare control samples under the same conditions as shown above, thereby giving hard capsule formulations for comparison.

The capsule formulations thus prepared were evaluated for their heat stability. In the heat stability test, each sample was stored in the dark at 50°C for 3 months while periodically measuring % active ingredient remaining in the capsules by high performance liquid chromatography, assuming that the value at the start of the test was set to 100%.

As shown in Figure 1, it is apparent that the formulation according to the present invention has improved stability because the decrease in % active ingredient is smaller than that observed in the control samples.

Example-2

1α-Hydroxycholecalciferol (10 mg) was dissolved in Coconad MT (1000 g, Kao Corporation) in the dark under a nitrogen gas stream and then encapsulated in the same manner as shown in

Example-1 to give a hard capsule formulation.

For comparison purposes, ODO mentioned above was used instead of Coconad MT to prepare a control sample under the same conditions as shown above, thereby giving a hard capsule formulation as the control samples.

The capsule formulations thus prepared were evaluated for their light stability. In the light stability test, each sample was wrapped in a UV-screening film (a UV-3 vinyl chloride film commercially available from Sumitomo Bakelite Co., Ltd.) and stored at room temperature (27°C) under a fluorescent lamp (1,000 Lux diffuse light) up to a cumulative total of 600,000 Lux·hr (Pharmacy, 1983) while periodically measuring % 1α-hydroxy-cholecalciferol remaining in the capsules by high performance liquid chromatography, assuming that the value at the start of the test was set to 100%. As shown in Figure 2, it is apparent that the formulation according to the present invention has improved stability because the decrease in % active ingredient is smaller than that observed in the control sample.

4. Brief Description of Drawings

Figure 1 shows heat stability of the hard capsule formulation according to the present invention. Figure 2 shows light stability of the hard capsule formulation according to the present invention.

Translation of Figures

Figure 1 (Heat stability)

Vertical axis:	% Active ingredient
Horizontal axis:	Months of storage
Open circle:	Present invention
Open square:	Control (ODO)
Solid circle:	Control (peanut oil)

Figure 2 (Light stability)

Vertical axis:	% Active ingredient
Horizontal axis:	Days of storage
Open circle:	Present invention
Open square:	Control